Paclitaxel, Bleomycin, Etoposide, and Cisplatin (T-BEP) as initial treatment in patients with poor-prognosis germ cell tumors (GCT): A phase II study.

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First line treatment of patients pts with poor-prognosis GCT, using BEP, is unsatisfactory. T-BEP (paclitaxel followed by BEP) demonstrated promising efficacy in the group of pts with intermediate and poor prognosis GCT. We present the results achieved with 1st line T-BEP in pts with poor-prognosis CGT. Twenty-four pts received T-BEP as initial therapy. Three pts (12.5%) had primary mediastinal GCT. Four cycles of T-BEP were given 21 days apart. Paclitaxel 175mg/m^2 was administered on day 1 before administration of BEP. The administration of G-CSF was not scheduled. Surgical resection of all radiographic residua was considered. All pts were assessable for response. Complete or partial response with negative tumor markers was achieved in 13 pts (54.2%; CI 95%: 34.3-74.1%). Median follow-up is 35.6 months. Median survival was not achieved and median time-to-progression is 9.5 months. Myelosuppression was the major toxicity with Gr3-4 granulocytopenia experienced in 52.1% of all courses. There were two treatment-related deaths due to sepsis. Patients treated with 1st line T-BEP didn't achieve higher response rate or time to progression. However, the overall survival observed in our study is surprisingly long. We do not recommend using this regimen without G-CSF support due to substantial toxicity.

Key words: *poor-prognosis germ cell tumors, paclitaxel, T-BEP*

Germ cell tumors (GCT) belong to the most chemosensitive solid tumors and represent a model of curable malignancy [1]. Cisplatin represents the mainstay in treatment of GCTs and about 70%-80% of patients (pts) with disseminated testicular cancer can be cured with 1st line cisplatin-based chemotherapy [2, 3]. However, pts with disseminated testicular cancer comprise very heterogeneous group according to their long-term survival and this was a reason for search of prognostic factors that could stratify patients to prognostic groups. Since 1997, the International Germ Cell Cancer Collaborative Group has classified patients with nonseminoma GCT according to localization of primary tumor site, extent of metastatic disease and level of serum tumor markers into the three prognostic groups with 5-year survival of 92%, 80% and 48% for good, intermediate and poor prognostic group, respectively [4].

Because of insufficient results in the treatment of poor-prognosis nonseminoma GCTs, evaluation of new treatment strategies and novel drugs with significant antitumor activity, as a single-agent or combination, remains a priority. Nowdays, the standard treatment for poor-prognosis group of patients is 4 cycles of BEP (bleomycin, etoposide, cisplatin) [4]. BEP was demonstrated to be more efficient than PVB (cisplatin, vinblastine, bleomycin) [5]. Attempts to increase the efficacy of BEP with double dose of cisplatin [6] or usage of ifosfamide in 1st line treatment (VIP- ifosfamide, etoposide, cisplatin) were, however, not successful and the higher toxicity of these new regimens was demonstrated [7]. Promising results with high-dose treatment (HD-CT) in 1st line treatment of poor-prognosis GCTs were demonstrated in phase II studies and retrospective matched-paired analysis, however recent prospective phase III study did not confirmed benefit of HD-CT [8, 9]. The same is true for alternating regimens as are POMB-ACE (POMB-cisplatin, vincristine, methotrexat, bleomycin; ACE-actinomycin D, cyclofosfamid, etoposide) and BOP-CISCA-POMB-ACE (BOP-bleomycin, vincristine, cisplatin; CISCA-cisplatin, cyclophosphamide, doxorubicin; POMB-cisplatin, vincristine, methotrexate, bleomycin; ACE-

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etoposide, dactinomycin, cyclophosphamide), where promising results were demonstrated only in phase II trials [10, 11]. Comparison of alternating regimen PEB/PVB or CISCA/VB with standard BEP did not bring improvement in efficacy [12, 13].

Single agent paclitaxel was studied in number of phase II studies of refractory GCTs at several centers with response rates ranging from 11 to 26% and high efficacy was demonstrated in the treatment combination TIP (paclitaxel, ifosfamide, cisplatin) [2, 14–19].

T-BEP (paclitaxel followed with standard BEP) was demonstrated as effective in the phase I/II trial in the 1st line treatment of pts with intermediate and poor prognosis GCTs, where all 13 evaluated pts achieved complete response and none of them relapsed within median follow-up period of 18 months [20]. Phase III EORTC trial comparing standard BEP with T-BEP in 1st line treatment of the pts with intermediate prognosis GCT is now ongoing.

Based on the results from the studies in salvage treatment and 1st line treatment of pts with intermediate prognosis, we decided to study efficacy and toxicity of T-BEP combination in 1st line treatment of male pts with poor prognosis GCTs. The primary endpoint of our study was objective response rate (ORR) and secondary endpoints were time to progression, overall survival (OS) and toxicity of the treatment.

We hypothesized that use of T-BEP combination in 1st line treatment will enhance efficacy that is achieved with standard treatment BEP in the treatment of poor-prognosis male pts with nonseminoma.

Patients and Methods

Eligibility. Twenty-four consecutive patients with diagnosis of nonseminoma GCT in IIIC stage were registered into this prospective, open-labeled, uncontrolled, non-randomized, unicentric, single-stage phase II clinical trial between May 2001 and May 2005.

All male pts with poor-prognosis nonseminoma GCT who were scheduled for 1st line treatment and fulfilled eligibility criteria (Table 1) were approved for this study. Diagnosis of nonseminoma GCT was accomplished by histology or clinical findings together with serum concentrations of tumor markers (AFP and/or b-HCG).

The study protocol and informed consent/patient information was reviewed and approved by the Scientific Board and Ethical Committee of the National Cancer Institute in Bratislava, Slovakia.

Pretreatment evaluation. Pretreatment evaluation included medical history, physical examination, ECG, complete cell blood count, 12-hour urine collection for determination of creatinine clearance rate, measurement of serum tumor markers (LDH, AFP, HCG), serum screening biochemistry panel, and computed tomograms of the chest, abdomen, and/or pelvis. In case of neurological symptomatology CT or MRI of CNS was realized. Bone-scan was scheduled only in the presence of skeletal symptomatology.

Treatment program. Treatment consisted of four cycles of T-BEP given 21 days apart. Paclitaxel 175mg/m^2 was administered on an inpatient basis by 3-hour infusion on day 1 after standard pre-medication that consisted of dexamethason, bisulepin-HCl, and ranitidine. Standard BEP combination was given after paclitaxel and consisted of cisplatin 20mg/m^2 and etoposid 100mg/m^2 given on day 1 through 5; and bleomycin 30mg/m^2 given on day 2, 8 and 15.

Standard antiemetic and hydration protocols were used. Haemopoetic growth factors were not scheduled. If febrile neutropenia and/or neutropenia Gr4 and/or trombocytopenia Gr4 and/or any non-hematological or renal toxicity Gr4 oc-

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
1. Patients older than 18 years.
2. Evidence of NSGCT based on histologic examination or on clinical evidence and elevated serum HCG or AFP levels (in case of clinical emergency, therapy can be started before pathologic sample is obtained if tumor markers are highly elevated)
3. Testicular, retroperitoneal, or mediastinal primary site.
4. Disease classified as poor prognosis according to IGCCCG criteria:
– Primary mediastinal NSGCT or
– Non-pulmonary visceral metastases or
– HCG > 50,000 UI/l, or AFP > 10,000 ng/ml, or LDH > 10 times the upper normal value.
5. No prior chemotherapy.
6. No concurrent treatment with experimental drugs.
7. No previous malignancy, except for basal-cell carcinoma of the skin.
8. Absolute granulocyte count 3 1,500/mm^3, platelets 3 100,000 mm^3, bilirubine L 1.5x the upper limit of normal value (exemption are patients with Gilbert disease), serum transaminases <5xULN.
9. Signed informed consent.
Exlusion criteria:
1. Patients who do not fit inclusion criteria.
2. Sexually active men not using effective birth control if their partners are women of childbearing potential.
3. Female patients.

curred, the doses of all three drugs were held and in the case of febrile neutropenia in the previous treatment cycle, hemopoetic growth factor filgrastim was used in the next cycle. The treatment was discontinued in case of neurotoxicity Gr4. The doses held due to toxicity or missed were not given at a later time. The patients who could not received drugs for more than 6 weeks from the time of the last treatment were discontinued from the study.

Evaluation of Response and Toxicity. Physical examination was performed and vital signs were assessed before each cycle or as indicated. Cell blood counts, serum screening biochemistry panel and serum tumor markers (LDH, AFP, HCG) were checked before each cycle and one month after the first day of the last cycle. After the completion of four cycles of chemotherapy, computed tomograms of the chest, abdomen, and/or pelvis were performed for assessment of tumor response. Surgical resection of all residual masses was considered.

Table 2. Patient's characteristics (n= 24)

	No.	%
Median of age (range)	30 (19 – 49)	
Primary tumor		
Gonadal	19	79.2
Retroperitoneal	3	12.5
Mediastinal	2	8.3
Sites of metastases		
Lungs	19	79.2
Liver	16	6.7
Brain	1	4.2
Mediastinum	13	54.2
Retroperitoneum	21	87.5
Other	8	33.3
Histology (pure)		
Embryonal carcinoma	11 (1)	45.8
Teratocarcinoma	12 (1)	50-0
Yolk sac	8 (2)	33.3
Choriocarcinoma	4 (1)	16.7
Mixed	12	50
No. of metastatic site		
1	3	12.5
2	3	12.5
More than 3	18	75
Elevation of tumor markers	24	96
LDH	18	75
AFP	19	76
HCG	19	80
Median (range) level of pretreatment tumor markers		
AFP mIU/ml	164 (31 – 8250)	
HCG mIU/ml	1493 (80 – 14320)	
LDH (μkat/l)	12 (9 – 121)	

Abbreviations: HCG, human chorionic gonadotropin; AFP, alfa fetoprotein; LDH, lactate dehydrogenase

A favorable response was classified as a complete response (CR) or a partial response, with negative serum tumor markers (PRnm-). A complete response to chemotherapy alone was defined as a disappearance of all clinical, radiographic, and biochemical evidence of disease for at least 4 weeks; this included patients in whom surgical resection of residuum yielded necrotic debris, fibrosis, or mature teratoma, but no evidence of viable malignant tumor. A complete response to chemotherapy plus surgery (sCR) was defined as a complete excision of all masses, at least one of which contained viable malignant tumor. An unfavorable response was classified as achievement of partial remission and failure of serum tumor marker normalization (PRnm+). The treatment was stopped and the patient was classified as having progressive disease in case of significant marker (more than 50%) and/or radiological progression (more than 25%) after one cycle. Time to progression and survival were measured from the initiation of therapy. Follow-up was measured from the initiation of treatment to end of trial evaluation. For toxicity evaluation NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) was used (http://www.fda.gov/cder/cancer/toxicityframe.htm).

Statistical consideration. Primary endpoint was response rate. The single-stage phase II study design to test the null hypothesis that P<=0.500 versus the alternative that P>=0.750 had an expected sample size of 23.

23 subjects are required in the study for decision whether the proportion responding, P, is less than or equal to 0.500 or greater than or equal to 0.750. If the number of responses is 16 or more, the hypothesis that P <= 0.500 is rejected with a target error rate of 0.050 and an actual error rate of 0.047. If the number of responses is 15 or less, the hypothesis that P >= 0.750 is rejected with a target error rate of 0.200 and an actual error rate of 0.196. For statistical analysis NCSS and Pass Number Cruncher Statistical Systems Utah (www.ncss.com) is used.

Results

Patient's Characteristics. Twenty-four male patients with nonseminoma GCT in the initial IIIC stage and median 30 years of age (range: 19–49) were included in the trial. S3 serum level of tumor markers had 16 pts (64%). Patient's characteristics are summarized in the Table 2. Five pts (20.8%) had extragonadal GCT and three of them (12.5%) had primary mediastinal tumor. Median number of metastatic sites was 3 (range 1–5).

Median number of treatment cycles given was 4 (range: 1–6). Five pts received less than 4 cycles of treatment combination T-BEP due to toxicity (1 pt: treatment-related death, 2 pts: hepatotoxicity Gr 3/4, 2 pts: septic complications). Six (25%) patients received more than 4 cycles of treatment combination T-BEP (TEP) with intention to achieve normalization of tumor markers level. Median dose intensity of paclitaxel, cisplatin and etoposide was 95% (range: 48%–108%), 96% (range: 78%–135%) and 93.5% (range: 78%–127%), respectively.

Response and Survival. All 24 patients were assessable for final analysis of overall survival on an intention-to-treat basis. The results of patient's response to treatment are summarized in Table 3. Kaplan-Meier event-free and overall survival curves are presented in the Figures 1 and 2.

No any patient achieved disappearance of all signs of disease during chemotherapy. Partial remission with negative serum markers was achieved by chemotherapy in 13 (54.2%) pts (CI 95%: 34.3–74.1%). Postchemotherapy retroperitoneal lymphadenectomy was realized in 5 pts and postchemotherapy thoracotomy in one patient. All resected tissue containted teratoma, fibrosis or necrosis and no malignant tissue was present. Thus five patients (20.8%) achieved CR. Eight patients (33,3%) patients achieved PRnm- as a definitive response.

No disease progression in the course of treatment was observed. There were two treatment related deaths due to septic shock, one with ARDS and one with toxic megacolon during the first and fourth treatment cycle, respectively.

Median follow-up was 35.6 months (range: 13–62 months). Median TTP was 9.5 months (ci 95%: 3.7-6.6 months). Median survival was not achieved and 75% of the patients survive more than 30.8 months.

Two pts with PRnm- (2/13, 15.4%) relapsed with time-to-progression (TTP) of 9.2 and 9.6 months. Both patients relapsed in CNS and are long-term survivors after one salvage treatment with survival of 43.5 and 33.5 months. None of the patients who achieved CR or PRnm- died of disease progression, but one of them died during the 4th treatment cycle due to febrile neutropenia with septic shock and toxic megacolon.

All pts with PRnm+ progressed during follow-up with median TTP of 5 months (range: 4-9 months). Four of them died due to disease progression and six of them are long-term survivors after one line of salvage treatment.

There were 3 pts with primary mediastinal tumor. One of them achieved CR and is a long-term survivor (48.8 months). Second pt achieved PRnm- with TRD during the forth treatment cycle due to septic shock. Third pt achieved PRnm+ with progression in the lungs and mediastinal lymph nodes after 7.8 months and died at 13.4 month from the start of the 1st line treatment. S3 level of markers had 15 pts and 40% (2/5), 50% (4/8), 78% (7/9) achieved CR, PRnm- and PRnm+, respectively. One pt with S3 died due to septic shock on 11th day of 1st treatment cycle.

In our study, the alternative hypothesis was not confirmed and response rate of 75% was not achieved with T-BEP in 1st line treatment combination of the pts with poor-prognosis GCT.

Toxicity. Toxicity Grade 3 and 4 of T-BEP in our patient's group is summarized in Table 4. Totally, 94 treatment cycles were administered.

Myelosupression with granulocytopenia was the major toxicity. The highest frequency of febrile neutropenia was during the 1st treatment cycle, when 20 (83%) pts had this type of complication. Febrile neutropenia was complicated with septic shock and respiratory failure with necessity of assisted pulmonary ventilation in one pt. Two patients (8.3%) developed septic shock, one with toxic megacolon during the 4th treatment cycle, and one with ARDS and respiratory failure during the 1st treatment cycle. Both of them died. Trombocytopenia gr.3/4 with need of platelet transfusions was most common during the 1st treatment cycle, when 11 pts (46%) experienced this type of complication.

Non-hematological toxicity gr. 3/4 was hepatotoxicity, diarrhea and mucositis in 1.9, 3.8 and 1.9% cycles, respectively. Hepatotoxicity led to discontinuation of paclitaxel in T-BEP treatment combination in two patients. There was only Gr.1/2 nausea and vomiting experienced during treatment and standard antiemetics were successful in management of this complication.

Discussion

The results of the 1st line treatment in the group of patients with poor-prognosis GCT are not satisfactory. According to data gained by international group in 5,862 patients with

Table 3. Response to Treatment

	No. of Patients	% (CI 95%)
Assessable	24	100.00
Favorable response	13	54.2 (34.3-74.1)
Complete response	5	20.1
Partial response with normalized markers (PRnm-)	8	33.3
Unfavorable response		
PRnm+	9	37.5 (18.3-56.7)
TRD (treatment related death)	2	8.3
Progression	0	0

Table 4. Main Grade 3 or 4 Toxicity during 94 treatment cycles According to NCI-CTC (Version 2.0) Classification:

	Number of cycles	% of cycles
Nonhematologic		
Nausea or vomiting	0	0
Hepatotoxicity	2	2.1
Diarrhea	2	2.1
Mucositis	4	16.7
Nefrotoxicity	0	0
Hematologic		
Granulocytopenia	49	52.1
Thrombocytopenia	11	11.7
Anemia	13	13.8
Febrile neutropenia	26	27.7
Treatment-related deaths	2	–

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria.

a median follow-up time of 5 years, 5-year DFS and overall survival in poor-risk category, that comprised 16% of all patients, was 41% and 48%, respectively [4]. However, the cure rate with standard BEP is probably 10% higher, because there were included even patients treated with older and less efficient regimens, as well. Because of insufficient results in poor-risk group of patients, there were efforts to increase the efficacy of BEP. Double dose of cisplatin was not demonstrated as being more efficient than standard dose, however regimen with double dose of cisplatin was more toxic [6]. VIP did not show statistically significant improvement in efficacy when compared with BEP, and 2-year overall survival was 63% versus 80% with VIP versus BEP, respectively [7].

Other approaches used were dose-dense and alternating therapeutic regimens, and high-dose treatment. There are negative data from three clinical trials with alternating therapeutic regimens. In EORTC trial, PEB was compared with PEB/PVB [12], in EORTC/MRC trial BEP/EP was compared to BOP/VIP-B [21] and in GETUG trial BEP was compared to CISCA/VB [13].

Dose-dense regimens were examined in non-randomized, phase II trials and demonstrated promising efficacy, however substantial toxicity. Three-year overall survival with POMB-ACE was 75% [11] and 73% with BOP-CISCA-POMB-ACE [10]. Randomized phase III trial comparing standard treatment with high-dose chemotherapy in 1st line did not confirmed promising results that were demonstrated in phase II studies and retrospective matched-pair analysis [8, 9].

Four cycles of BEP are considered as a standard 1st line treatment in the patients with intermediate and poor-prognosis GCT.

The introduction of new effective drugs in the treatment of poor-prognosis GCT could be real hope for this group of pts. Paclitaxel showed substantial efficacy in salvage treatment in monotherapy, as well as in combination [2, 14–19]. In phase I/II trial T-BEP demonstrated treatment efficacy with manageable toxicity in pts with intermediate and poor-prognosis [20]. All 13 pts included in this trial achieved complete response. With a median follow-up of 18 months, none of these patients relapsed. According to these results, a randomized phase II/III study of T-BEP (with so-called standard dose of paclitaxel) versus BEP in intermediate-risk patients has been commenced by EORTC.

In our study, we used the T-BEP regimen only in the group of pts with poor prognosis. We present the results achieved in 24 patients. Two of them had primary mediastinal germ cell tumor and 18 of them had more than 3 metastatic sites. The favorable response was achieved only in 13 patients (54,2%). Five of them (20,8%) achieved complete response and 8 patients (33,3%) achieved PRnm-. None of these patients died during median follow-up of 35,6 months. However two of the patients with PRnm- relapsed in CNS, and they achieved complete remission with one salvage therapy (WBRT with four courses of VIP) and are currently alive without disease.

The number of durable responses achieved in our study is comparable with the results reported in larger studies with standard therapy that consisted of 4 x BEP. However the overall survival observed in our study is surprisingly long. Median survival has not been achieved and 75% of these poor-prognosis pts survive more than 30 months. The discrepancy between number of remissions and long-term survival is caused by unusual efficacy of salvaged treatment in patients who did not achieved favorable response with T-BEP regimen. Five out of nine patients, who did not achieve favorable response with T-BEP, responded on salvage therapy based on ifosfamide and cisplatin. Four of them survive without disease 27.7, 37.7, 49.4 and 60.1 months, and 1 patient died at 18,6 month due to disease progression. We cannot explain high efficacy of cisplatin-based salvage regimen in pts generally considered as refractory to 1st line cisplatin-based treatment. All these pts did not achieve normal level of serum markers by primary treatment and they progressed within 4–6 months after T-BEP therapy. This observation is contradictory with result observed in DE WITT study [20] and it could be caused by low number of patients in our study. Another explanations could be the influence of possible antagonism between etoposide and paclitaxel, which was observed in in-vitro studies [22–24], or possible synergistic effect of sequential treatment of T-BEP and VIP [25]. These phenomena require further investigation.

The toxicity of T-BEP regimen was high. The main toxicity was granulocytopenia and thrombocytopenia. G-CSF was not scheduled as a part of therapeutic regimen and it contributed to high incidence of granulocytopenia and febrile neutropenia. Eighty percent of pts had grade 3–4 granulocytopenia in 1st cycle of therapy. The incidence of febrile neutropenia in later cycles of the treatment was low. Only 5 pts experienced febrile neutropenia during 2nd – 5th cycle. We do not recommend using T-BEP regimen without G-CSF.

Patients treated with 1st line T-BEP didn't achieve higher response rate or time to progression. However, the overall survival observed in our study is surprisingly long and is comparable with the results achieved in phase II trials with dose-dense and high-dose therapy.

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